



**University of  
Zurich**<sup>UZH</sup>

**Zurich Open Repository and  
Archive**

University of Zurich  
University Library  
Strickhofstrasse 39  
CH-8057 Zurich  
[www.zora.uzh.ch](http://www.zora.uzh.ch)

---

Year: 2017

---

**Investigating biogenetic hypotheses of the securinega alkaloids:  
enantioselective total syntheses of secu'amamine E/ent-virosine A and  
bubbialine**

Wehlauch, Robin ; Grendelmeier, Simone M ; Miyatake-Ondozabal, Hideki ; Sandtorv, Alexander H ;  
Scherer, Manuel ; Gademann, Karl

**Abstract:** The synthesis of the Securinega alkaloid secu'amamine E (ent-virosine A) has been accomplished for the first time in 12 steps and 8.5% overall yield. In addition, bubbialine has been prepared and characterized. These two alkaloids and bubbialidine, all featuring an azabicyclo[2.2.2]octane core, were rearranged to their azabicyclo[3.2.1]octane congeners, a framework found in many Securinega alkaloids. These experiments suggest that azabicyclo[2.2.2]octane derivatives could serve as intermediates in the biosynthesis of the rearranged azabicyclo [3.2.1]octane products.

DOI: <https://doi.org/10.1021/acs.orglett.6b03716>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-138852>

Journal Article

Accepted Version

Originally published at:

Wehlauch, Robin; Grendelmeier, Simone M; Miyatake-Ondozabal, Hideki; Sandtorv, Alexander H; Scherer, Manuel; Gademann, Karl (2017). Investigating biogenetic hypotheses of the securinega alkaloids: enantioselective total syntheses of secu'amamine E/ent-virosine A and bubbialine. *Organic Letters*, 19(3):548-551.

DOI: <https://doi.org/10.1021/acs.orglett.6b03716>

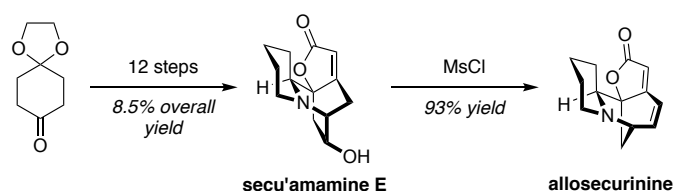
# Investigating Biogenetic Hypotheses of the *Securinega* Alkaloids: Enantioselective Total Syntheses of Secu'amamine E/ent-Virosine A and Bubbialine

Robin Wehlauch,<sup>†,‡</sup> Simone M. Grendelmeier,<sup>†</sup> Hideki Miyatake-Ondozabal,<sup>‡,§</sup> Alexander H. Sandtorv,<sup>‡,¶</sup> Manuel Scherer,<sup>†,‡</sup> and Karl Gademann<sup>\*,†</sup>

<sup>†</sup>Department of Chemistry, University of Zurich, 8057 Zurich, Switzerland

<sup>‡</sup>Department of Chemistry, University of Basel, 4056 Basel, Switzerland

Supporting Information Placeholder



**ABSTRACT:** The synthesis of the *Securinega* alkaloid secu'amamine E (*ent*-virosine A) has been accomplished for the first time in 12 steps and 8.5% overall yield. In addition, bubbialine has been prepared and characterized. These two alkaloids and bubbialidine, all featuring an azabicyclo[2.2.2]octane core, were rearranged to their azabicyclo[3.2.1]octane congeners, a framework found in many *Securinega* alkaloids. These experiments suggest that azabicyclo[2.2.2]octane derivatives could serve as intermediates in the biosynthesis of the rearranged azabicyclo[3.2.1]octane products.

The *Securinega* alkaloids consist of a group of more than 60 known secondary metabolites isolated from plants of several genera of the Phyllanthaceae family, including *Securinega*, *Phyllanthus*, *Flueggea* and others.<sup>1</sup> Some of these plants have been used in traditional folk medicines across Asia, Africa and Amazonia, and subsequently, several compounds of the family were shown to exhibit antimalarial, antibacterial, antitumor as well as central nerve system activities.<sup>1,2</sup> Among the *Securinega* alkaloids, securinine constitutes the most abundant and best-studied representative featuring the securinane skeleton (Scheme 1A), and the group includes a series of isomeric neosecurinane-type and two lower homologs of norsecurinane- and neonorsecurinane-type, respectively (see Scheme 1A for an overview). Structurally, these compounds can be divided in groups featuring either azabicyclo[2.2.2]- or azabicyclo[3.2.1]octane BC ring systems with a fused pyrrolidine or piperidine ring. Their interesting biological activities combined with the bridged tetracyclic core structure triggered numerous synthetic efforts toward *Securinega* alkaloids.<sup>1,2c,3,4</sup>

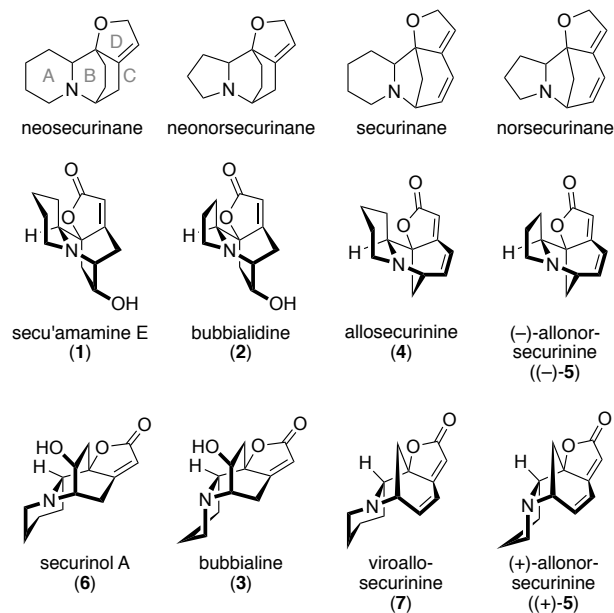
Secu'amamine E (**1**) was isolated along with two new congeners from *Securinega suffruticosa* var. *amamiensis* by Ohsaki *et al.* in 2009<sup>5</sup> and constitutes a member of the neosecurinane series. The enantiomer *ent*-**1** has also been isolated as virosine A from *Flueggea virosa*,<sup>6</sup> although this relationship was not revealed in the subsequent.<sup>5</sup> The lower homolog of **1**, bubbialidine (**2**), the synthesis of which we have reported recently,<sup>7</sup> belongs to the neonorsecurinane

family and was isolated along with the isomeric bubbialine (**3**).<sup>8</sup> While allosecurinine (**4**) is a natural epimer of securinine, neither enantiomer of allonorsecurinine (**5**) has been obtained from a natural source, in contrast to securinol A (**6**) and viroallosecurinine (**7**).<sup>9</sup>

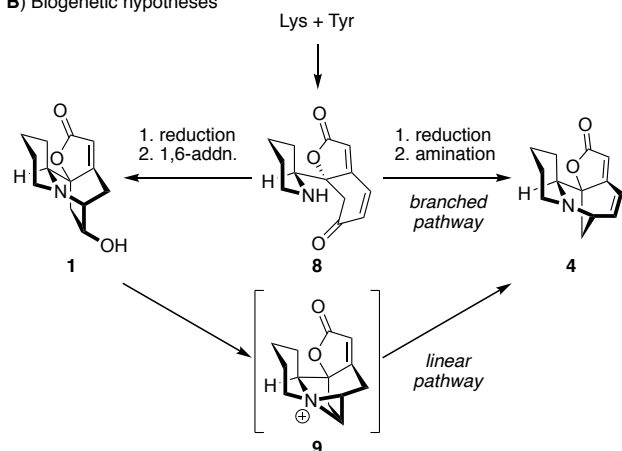
The biosynthetic origin of both the A ring and the C/D system has been investigated over decades,<sup>10</sup> and can be traced back to lysine and tyrosine catabolites, which merge to the postulated tricyclic intermediate **8** (Scheme 1B). The origin of the B/C bicyclic ring system however, received much less attention, and therefore remains an interesting subject for scientific investigation. The general biosynthetic pathway formulated in the 1970s suggested that intermediate **8** can either react *via* reduction and 1,6-addition to the azabicyclo[2.2.2]octane system to form *e.g.* **1**, or *via* reduction and amination to the azabicyclo[3.2.1]octane system to directly afford **4**.<sup>10</sup> An alternative biogenetic hypothesis suggests that compounds featuring the azabicyclo[2.2.2]octane ring system **1** could be *intermediates*, of which the azabicyclo[3.2.1]octane compounds of type **4** would result through subsequent rearrangement involving an aziridinium ion such as **9**, which has already been postulated by Horii *et al.* in the 1960s.<sup>11</sup> This hypothesis has, to the best of our knowledge, first been suggested by Magnus *et al.* in 1993,<sup>12</sup> but later received little attention,<sup>4g</sup> and recent review articles do not mention this mechanistic possibility.

**Scheme 1. General structures and biogenetic hypotheses of *Securinega* alkaloids.**

**A) *Securinega* alkaloid structures**



**B) Biogenetic hypotheses**

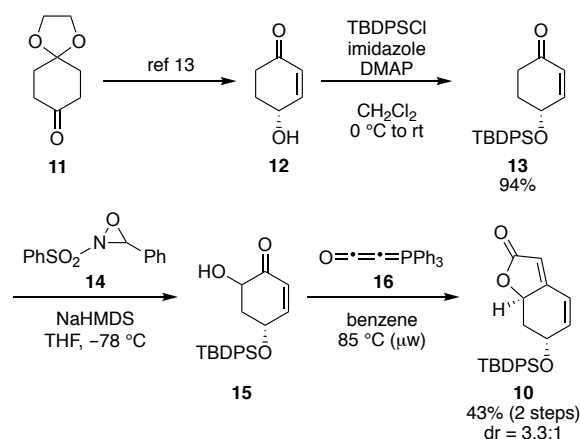


In this study, we provide experimental evidence for the second hypothesis by converting three different azabicyclo[2.2.2] natural products to the rearranged azabicyclo[3.2.1] congeners. Along these lines, the first total syntheses of secu'amamine E/ent-virosine A (**1**) and bubbialine (**3**) are reported.

Analogous to our earlier work,<sup>7</sup> the key intermediate in our synthesis of secu'amamine E (**1**) is TBDPS-protected (+)-aquiilegionolide (**10**), for which a shorter synthesis was developed (Scheme 2). Ketal **11** was transformed into enone **12** in four steps and 37% overall yield following procedures developed by Hayashi *et al.* during their total synthesis of (+)-panepophenanthrin.<sup>13</sup> To this goal, a proline-catalyzed stereoselective  $\alpha$ -addition of nitrosobenzene, a reduction of the ketone using K-selectride followed by reductive N-O cleavage and finally an acid-catalyzed ketal hydrolysis with concomitant elimination of water led to the desired  $\gamma$ -hydroxy enone **12**. The hydroxyl function was protected with a TBDPS group to give fully protected enone **13** in 94% yield. For the subsequent  $\alpha$ -hydroxylation, we first investigated the use of Rubottom oxidation conditions.<sup>14</sup> While <sup>1</sup>H NMR analyses indicat-

ed clean formation of the corresponding silyl enol ethers using either TMSCl or TESCl and NaHMDS, the subsequent reaction with *m*CPBA led to decomposition of the substrate and complex mixtures were obtained. We then evaluated Davis' oxaziridines as oxidants and treatment of the pre-formed sodium enolate with 3-phenyl-2-(phenylsulfonyl)oxaziridine (**14**)<sup>15</sup> at  $-78^\circ\text{C}$  yielded  $\alpha$ -hydroxy ketone **15**. In addition, a clean formation of the product was also observed when a mixture of enone **13** and oxaziridine **14** in THF at  $-78^\circ\text{C}$  was reacted with NaHMDS. However, isolation and purification turned out to be difficult, as enone **15** was not stable during flash column chromatography. Moreover, *N*-benzylidenebenzenesulfonamide, the byproduct formed from oxaziridine **14**, displayed very similar retention properties on silica as the hydroxy ketone **15**. When instead (+)-(8,8-dichlorocamphorylsulfonyl)oxaziridine was used to generate a different byproduct, none of the desired product **15** was detected. The best results were obtained by washing the organic fraction with aqueous NaHSO<sub>3</sub>, therefore removing most of the imine and aldehyde contents, and followed by filtration with apolar solvent to remove insoluble benzenesulfonamide. To setup the butenolide D ring, we applied an efficient one-pot addition/Wittig reaction sequence using the Bestmann ylide ((triphenylphosphoranylidene)ketene, **16**).<sup>16</sup>  $\alpha$ -Hydroxy enone **15** was heated in benzene in the presence of ketene **16** to give the bicyclic key intermediate **10** in 43% yield over two steps as a mixture of diastereoisomers (3.3:1), which was inconsequential and the isomers were thus not separated. While lower temperatures only slowed down the reaction, the addition of triethylamine did not have any impact on yield.

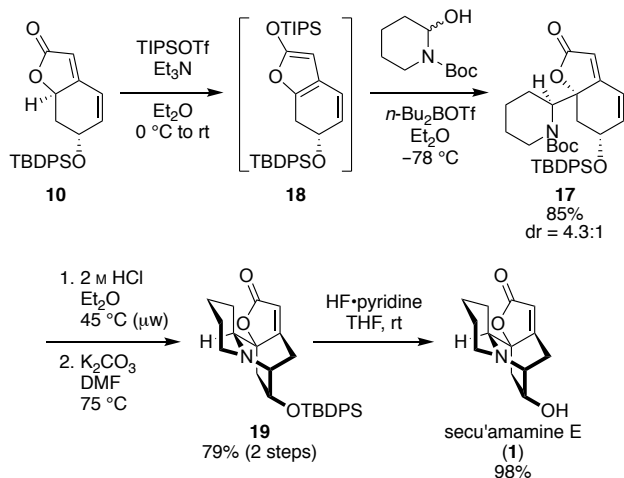
**Scheme 2. Synthesis of bicyclic key intermediate 7**



The A ring was introduced using a one-pot procedure reported by Busqué, de March *et al.* producing the desired product **17** in high yield and good selectivity (Scheme 3).<sup>17</sup> Since the reaction proceeds *via* silyl enol ether **18**, both diastereoisomers of intermediate **10** lead to the same product. The two diastereoisomers generated could be separated by silica column chromatography. The Boc protecting group was then removed with ethereal HCl solution at elevated temperature to give the desired hydrochloride in 97% yield. When the salt was heated in a suspension of dipotassium phosphate in DMF the desired tetracycle **19** was isolated in varying yields. Applying more basic potassium carbonate in this transformation afforded silyl ether **19** in a yield of 81%. Final deprotection of the hydroxyl function by treatment with excess HF·pyridine afforded secu'amamine E (**1**) in 98% yield. Thus, the neose-

curinane alkaloid **1** was synthesized in 12 steps in an overall yield of 8.5%. All analytical data obtained from the synthetic material were identical with those reported for the authentic natural product. The optical rotation of  $-45.7^\circ$  ( $c = 0.10$ , MeOH) of the synthetic alkaloid **1** matched the value of  $-43.8^\circ$  ( $c = 0.08$ , MeOH) reported by Ohsaki *et al.*<sup>5</sup>

### Scheme 3. Enantioselective synthesis of secu'amamine E

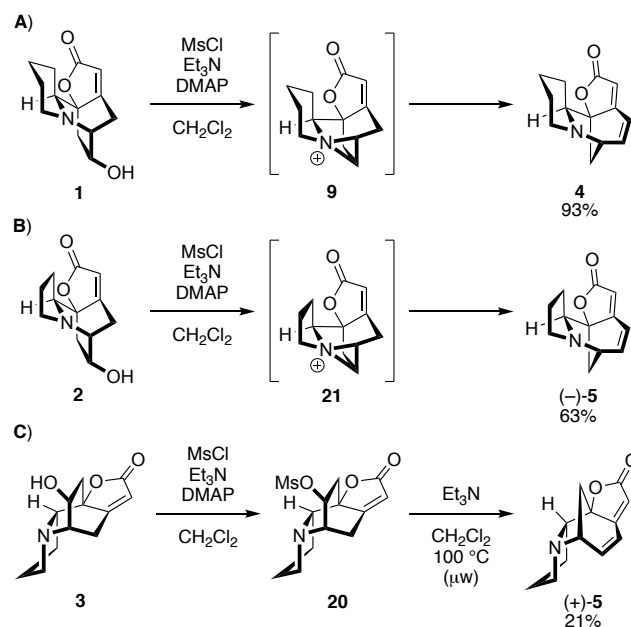


In order to profile the ecotoxicity of this alkaloid, we tested the synthetic material for toxicity against the freshwater crustacean *Thamnocephalus platyurus* (beavertail fairy shrimp).<sup>18</sup> In an acute toxicity assay, five concentrations of alkaloid **1** ranging from 1.23  $\mu$ M to 100  $\mu$ M were incubated with 10 animals for 24 h, each concentration in three separate experiments. Each experiment was evaluated by visual inspection of the animals before and after incubation. However, no toxicity of alkaloid **1** could be observed in this concentration range. In addition to secu'amamine E (**1**), we have obtained bubbialidine (**2**) and bubbialine (**3**) following a previously published route.<sup>7</sup> In this context, bubbialine (**3**) was characterized for the first time during this work.

We then focused on evaluating the feasibility of the hypothesis outlined above, *i.e.* if the azabicyclo[2.2.2]octane ring system **1** constitutes an *intermediate en route* to azabicyclo[3.2.1]octane compounds of type **4**. To test the generality of the dehydrative rearrangement outlined above in Scheme 1B, we treated synthetic samples of secu'amamine E (**1**), bubbialidine (**2**) and bubbialine (**3**) with MsCl in the presence of DMAP and Et<sub>3</sub>N. Alkaloids **1** and **2** reacted within seconds at room temperature to give the rearranged alkaloids allosecurinine (**4**) and (–)-allonorsecurinine ((–)-**5**), respectively, in up to 93% yield (Scheme 4A and B). In contrast, bubbialine (**3**) reacted to give the corresponding mesylate **20** under these conditions, which could be isolated and purified by chromatography on silica gel (Scheme 4C). To effect the rearrangement of the sulfonate **20**, forcing conditions had to be applied (100 °C, microwave, 6 h) and (+)-allonorsecurinine ((+)-**5**) was isolated in low yield and moderate purity. These experimental observations can be explained by the mechanistic rationale outlined in Scheme 4. Formation of the aziridinium intermediates **9** or **21** is highly favored for alkaloids with an *antiperiplanar* configuration of the amino and hydroxy groups on the C ring, as the nitrogen is well aligned to donate electron density into the  $\sigma^*$  orbital of the exocyclic C–O bond. Thus, the structure allows for rapid extrusion of the

mesylate *via* such a mechanism. However, when the groups are arranged in *synperiplanar* configuration, such as for **5**, this orbital interaction is less feasible and the mesylate has to leave in an S<sub>N</sub>1 fashion.

### Scheme 4. Dehydrative rearrangement of *Securinega* alkaloids



As a consequence of these mechanistic observations, we speculate that neosecurinane- and neonorsecurinane-type alkaloids possessing a [2.2.2]-bicyclic core serve as direct biosynthetic intermediates of securinane- and norsecurinane-type alkaloids with an unsaturated [3.2.1] core. Accordingly, the biosynthesis of  $\alpha,\beta,\gamma,\delta$ -unsaturated *Securinega* alkaloids would be extended by an additional intermediate featuring an OH group and thus follow a linear pathway (Scheme 1B). Based on the hypothesis by Busqué, de March *et al.*, intermediate **8** may also be formulated as an alcohol instead of the ketone.<sup>17</sup> Analogous to the transformation of **10** reported in Scheme 3, the tricyclic amine might derive naturally from the bicyclic lactones (+)-aquilegiolide and/or (+)-menisdaurilide *via* vinylogous Mannich reaction and thus already contain the hydroxy group.

In summary, we have completed the first enantioselective total synthesis of secu'amamine E (**1**) in 12 steps and 8.5% overall yield. Key transformations are a butenolide formation using the Bestmann ylide (**16**), a vinylogous Mannich reaction to introduce the A ring and an intramolecular aza-Michael addition to form the B ring. Furthermore, three synthetic natural products (**1**, **2** and **3**) featuring an azabicyclo[2.2.2]octane core were rearranged to their azabicyclo[3.2.1]octane congeners supporting a linear biogenetic hypothesis for *Securinega* alkaloids. Thus, neo(nor)securinane-type alkaloids with an *antiperiplanar* configuration on the C ring might serve as natural precursors of the (nor)securinane-type alkaloids.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: karl.gademann@uzh.ch.

### Present Addresses

<sup>§</sup>Bayer Pharma AG, Global Drug Discovery, Medicinal Chemistry, 42096 Wuppertal, Germany.

<sup>†</sup>Department of Chemistry, Portland State University, Portland, OR 97201, USA.

## ACKNOWLEDGMENT

We gratefully acknowledge partial financial support by the NCCR Molecular Systems Engineering, the Latsis Prize (to K.G.), and the Novartis Early Career Award (to K.G.). Andrea Meier (University of Basel) is gratefully acknowledged for skillful technical assistance.

## REFERENCES

- (1) Chirkin, E.; Atkalian, W.; Porée, F.-H. In *The Alkaloids*; Knölker, H.-J., Ed.; Academic Press: London, 2015; Chapter 1, pp 1–120.
- (2) (a) Raj, D.; Łuczkiwicz, M. *Fitoterapia* **2008**, *79*, 419–427. (b) Calixto, J. B.; Santos, A. R. S.; Cechinel-Filho, V.; Yunes, R. A. *Med. Res. Rev.* **1998**, *18*, 225–258. (c) Zhang, W.; Li, J.-Y.; Lan, P.; Sun, P.-H.; Wang, Y.; Ye, W.-C.; Chen, W.-M. *J. Chin. Pharm. Sci.* **2011**, *20*, 203–217.
- (3) Review: Weinreb, S. M. *Nat. Prod. Rep.* **2009**, *26*, 758–775.
- (4) For recent syntheses, see: (a) González-Gálvez, D.; García-García, E.; Alibés, P.; Bayón, R.; de March, P.; Figueredo, M.; Font, J. J. *Org. Chem.* **2009**, *74*, 6199–6211; (b) Medeiros, M. R.; Wood, J. L. *Tetrahedron* **2010**, *66*, 4701–4709; (c) Reddy, A. S.; Srihari, P. *Tetrahedron Lett.* **2012**, *53*, 5926–5928; (d) Bélanger, G.; Dupuis, M.; Larouche-Gauthier, R. J. *Org. Chem.* **2012**, *77*, 3215–3221; (e) Chen, J.-H.; Levine, S. R.; Buergler, J. F.; McMahon, T. C.; Medeiros, M. R.; Wood, J. L. *Org. Lett.* **2012**, *14*, 4531–4533; (f) Wie, H.; Qiao, C.; Liu, G.; Yang, Z.; Li, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 620–624; (g) Ma, N.; Yao, Y.; Zhao, B.-X.; Wang, Y.; Ye, W.-C.; Jiang, S. *Chem. Commun.* **2014**, *50*, 9284–9287; (h) Zheng, X.; Liu, J.; Ye, C.-X.; Wang, A.; Wang, A.-E.; Huang, P.-Q. *J. Org. Chem.* **2015**, *80*, 1034–1041.
- (5) Ohsaki, A.; Nagaoka, T.; Yoneda, K.; Kishida, A. *Tetrahedron Lett.* **2009**, *50*, 6965–6967.
- (6) Wang, G.-C.; Wang, Y.; Li, Q.; Liang, J.-P.; Zhang, X.-Q.; Yao, X.-S.; Ye, W.-C. *Helv. Chim. Acta* **2008**, *91*, 1124–1129.
- (7) Miyatake-Ondozabal, H.; Bannwart, L. M.; Gademann, K. *Chem. Commun.* **2013**, *49*, 1921–1923.
- (8) Ahond, A.; Guilhem, J.; Hamon, J.; Hurtado, J.; Poupat, C.; Pusset, J.; Pusset, M.; Sévenet, T.; Potier, P. *J. Nat. Prod.* **1990**, *53*, 875–881.
- (9) (a) Satoda, I.; Murayama, M.; Tsuji, J.; Yoshii, E. *Tetrahedron Lett.* **1962**, *3*, 1199–1206; (b) Saito, S.; Tanaka, T.; Iwamoto, T.; Matsumura, C.; Sugimoto, N.; Horii, Z.; Makita, M.; Ikeda, M.; Tamura, Y. *J. Pharm. Soc. Jpn.* **1964**, *84*, 1126–1133; (c) Horii, Z.; Ikeda, M.; Tamura, Y.; Saito, S.; Kotera, K. *Chem. Pharm. Bull.* **1965**, *13*, 1307–1311; (d) Horii, Z.; Yamawaki, Y.; Tamura, Y.; Saito, S.; Yoshikawa, H.; Kotera, K. *Chem. Pharm. Bull.* **1965**, *13*, 1311–1318.
- (10) (a) Parry, R. J. *Tetrahedron Lett.* **1974**, *15*, 307–310. (b) Sankawa, U.; Yamsaki, K.; Ebizuka, Y. *Tetrahedron Lett.* **1974**, *15*, 1867–1868. (c) Parry, R. J. *J. Chem. Soc., Chem. Commun.* **1975**, 144–145. (d) Golebiewski, W. M.; Horsewood, P.; Spenser, I. D. *J. Chem. Soc., Chem. Commun.* **1976**, 217–218. (e) Sankawa, U.; Ebizuka, Y.; Yamasaki, K. *Phytochemistry* **1977**, *16*, 561–563. (f) Parry, R. J. *Bioorg. Chem.* **1978**, *7*, 277–288.
- (11) (a) Horii, Z.; Ikeda, M.; Tamura, Y.; Saito, S.; Kotera, K.; Iwamoto, T. *Chem. Pharm. Bull.* **1965**, *13*, 1307–1311. (b) Horii, Z.; Yamauchi, M.; Ikeda, M.; Momose, T. *Chem. Pharm. Bull.* **1970**, *18*, 2009–2012.
- (12) Magnus, P.; Rodríguez-López, J.; Mulholland, K.; Matthews, I. *Tetrahedron* **1993**, *49*, 8059–8072.
- (13) Matsuzawa, M.; Kakeya, H.; Yamaguchi, J.; Shoji, M.; Onose, R.; Osada, H.; Hayashi, Y. *Chem. Asian J.* **2006**, *1*, 845–851.
- (14) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319–4322.
- (15) (a) Davis, F. A.; Lamendola, Jr., J.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, Jr., R.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000–2005; (b) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774–1775.
- (16) Bestmann, H. J.; Sandmeier, D. *Chem. Ber.* **1980**, *113*, 274–277.
- (17) Bardají, G. G.; Cantó, M.; Alibés, R.; Bayón, P.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. J. *Org. Chem.* **2008**, *73*, 7657–7662.
- (18) (a) Törökné, A. K.; László, E.; Chorus, I.; Sivonen, K.; Barbosa, F. A. R. *Environ. Toxicol.* **2000**, *11*, 549–553; (b) Nalecz-Jawecki, G.; Persoone, G. *Environ. Sci. & Pollut. Res.* **2006**, *13*, 22–27; (c) Kim, J.-W.; Ishibashi, H.; Yamauchi, R.; Ichikawa, N.; Takao, Y.; Hirano, M.; Koga, M.; Arizono, K. *J. Toxicol. Sci.* **2009**, *34*, 227–232; (d) Portmann, C.; Blom, J. F.; Gademann, K.; Jüttner, F. *J. Nat. Prod.* **2008**, *71*, 1193–1196; (e) Gademann, K.; Portmann, C.; Blom, J. F.; Zeder, M.; Jüttner, F. *J. Nat. Prod.* **2010**, *74*, 980–984; (f) Scherer, M.; Bezold, D.; Gademann, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 9427–9431.